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Acute Lymphoblastic Leukemia Detection in Microscopic Cell Images using Deep Learning Models

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ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is a cancer of the lymphoid line of blood cells characterized by the development of large numbers of immature lymphocytes. Extensive research has been done over the application of machine learning algorithms for detection of ALL but use of Deep Learning (DL) models is relatively scarce. In this paper, we evaluate and compare the available DL architectures with our proposed model for ALL classification and obtain better results as compared to existing ones.

Keywords: Acute Lymphoblastic Leukemia (ALL) · Cancer · Classification·Deep Learning.

1 INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [1][2]. Cancer has a major effect on societies worldwide as it is one of the leading causes of deaths. In 2015, about 90.5 million people were known to be cancer affected with about 14.1 million new cases occurring each year (not including skin cancer and other melanomas), and led to deaths of 8.8 million people [3][4][5]. Leukemia is one of the most common cases of cancers. Leukemias are cancers that start in cells that would normally develop into different types of blood cells. Most often, leukemia starts in early forms of white blood cells, but some leukemias start in other blood cell types. There are several types of leukemia, which are divided based mainly on whether the leukemia is acute (fast growing) or chronic (slower growing), and whether it starts in myeloid cells or lymphoid cells. Knowing the specific type of leukemia helps doctors better predict each person's prognosis (outlook) and select the best treatment [6].

Acute Lymphoblastic Leukemia (ALL) is a cancer of the lymphoid line of blood cells characterized by the development of large numbers of immature lymphocytes [7]. As an acute leukemia, ALL progresses rapidly and is typically fatal within weeks or months if left untreated [8]. Figure 1 shows the types of ALL (L1, L2, & L3) and Table 1 gives the types of ALL, along with the type of cells affected as well as characteristics of the affected cells. In 2015 there were 876,000 cases of ALL which resulted in 111,000 deaths. In 2019 there have been 5930 cases of ALL and 1500 deaths so far [9]. Diagnosing ALL begins with a thorough medical history, physical examination, complete blood count, and blood smears. Bone Marrow Biopsy. Lumbar Puncture & Medical Imaging (Metastasis). Pathological examination and Cytogenetics [10].

Lymphocytes are the main cells that make up lymph tissue, a major part of the immune system. Lymph tissue is found in lymph nodes, the thymus, the spleen, the tonsils and adenoids, and is scattered throughout the digestive and respiratory systems and the bone marrow. Lymphocytes develop from cells called lymphoblasts to become mature, infection-fighting cells. There are 2 main types of lymphocytes:

B lymphocytes (B cells):

B cells help protect the body by making proteins called antibodies. The antibodies attach to germs (bacteria, viruses, and fungi) in the body, which helps the immune system destroy them.

T lymphocytes (T cells):

There are several types of T cells, each with a special job. Some T cells can destroy germs directly, while others play a role in either boosting or slowing the activity of other immune system cells.

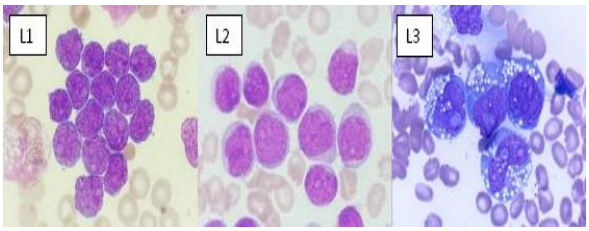

Fig.1: ALL types.

FAB Sub-Type	Cell-Type	Characteristics
ALL - L1	T cell or pre-B cell	Small and homogeneous (uniform) cells
ALL - L2	T cell or pre-B cell	Large and heterogeneous (varied) cells
ALL - L3	B cell	Large and varied cells with vacuoles

Table 1: ALL types with affected cell types and cell characteristics.

ALL develops from early forms of lymphocytes. It can start in either early B cells or T cells at different stages of maturity but the physical changes from normal cell to affected cell are imperceptible through ordinary methods.If the All cell does not develop the characteristic hand-mirror shape, the image profile of ALL cell and normal cell looks the same to human eye.

To correctly distinguish the affected cells from normal cells we followed deep learning approach so as to extract the minute differential features from the dataset during training and then computed the accuracy on the testing dataset. The first step was to train the existing deep learning architectures on our dataset and then compare their performance and later we devised our own model to improve upon the results from the existing architectures. Since transfer learning did not provide any improvement in the results all the models needed to be trained from scratch.

The paper is organized as follow, section II discuss similar related research. The challenges and contribution is presented in section III. The proposed approach is presented in Section IV. Section V analyses and discusses the experimental results. Finally, section VI presents our conclusion and section VII future work.

2 RELATED WORK

Effectiveness and robustness of learned CNN features have helped in achieving breakthroughs in the fields of image classification [11][12], contour detection [13] and object detection [14]. The previous models for automated ALL detection have proposed using machine learning models and have mostly used ALL-IDB dataset. Most of the present work done on this dataset has been on segmentation rather than classification.

Luis H. S. Vogado, Rodrigo de M. S. Veras, Alan R. Andrade, Flavio H. D. de Araujo in 2016 proposed a method [15] for Acute lymphoblastic leukemia segmentation using two color channels and unsupervised algorithm k means. Improvement in the technique, they intend to develop a classification step, so we can effectively conclude the creation of an automated detection system.

JakkrichLaosai and KosinChamnongthai [16] proposed a method for classifying leukemia by using cluster of differentiation (CD) method. The classification proposed 3 subtypes of ALL and 8 subtypes of AML that are characterized by unique morphologic, immunologic, and cytogenetic features Immunologic (MIC group) markers cluster of differentiation (CD). They get accuracy 93.89%. They also used SVM and k means algorithm [17]. The method has been evaluate using k means clustering. And they get 92% performance from SVM. They also used neural network for classification [18]. For this the different features are extracted from the input images and based on those features the dataset is created. Then the dataset is utilized as input data to a neural network for training purposes. This neural network is designed and created to categorize the images according to their corresponding leukemia type.

Faisal Asadi et.al. used a combination of back-propagation neural network and blood cells extraction imagery to classify acute leukemia. They used back-propagation neural network algorithm to extract the characteristics of blood cells ALL and AML and digital image processing for the leukemia identification technique. They were able to identify ALL and AML cases about 93.3% and 80%, respectively, and they achieved about 86.66% accuracy in classifying the leukemia acute types on average [19]. Ahmed et.al. used Elephant Herd Optimization with Feed Forward Neural Networks for ALL detection. They used various machine learning and deep learning techniques for classification purpose and achieved an accuracy of 91.8% [20].

3 CHALLENGES AND CONTRIBUTION

Although the efficiency and accuracy of DL models for image classification has already been shown by multiple researchers, classification still proves to be a challenging task. Additionally, applying transfer-learning from pre-trained models, i.e. trained on IMAGENET dataset, prove to be ineffective, leading to the models being completely trained from scratch.

Our aim is to study the applicability of different available DL architectures and to devise a new, better model/architecture for ALL detection from microscopic ALL histopathological images. These images are provided as input to the DL models which classify the images as ALL cells or normal cells.

4 Proposed Approach

In this Section we discuss all the methods that were employed for the classification purpose.

4.1 Initial Dataset Details

The initial dataset consists of cell images from 76 subjects of which 47 subjects suffer from ALL and the rest are healthy. The dataset consists of 10,661 images, with an image size of 450∗450, of which 7,272 images are classified as ALL, labelled “all”, and the remaining 3,389 have been classified as healthy cells, labelled “hem” [21]. Each training example/image consists of a single cell, pre-segmented with a black border. Furthermore, the two classes of cells share very close visual similarity. Some sample Images are shown in the figure below.

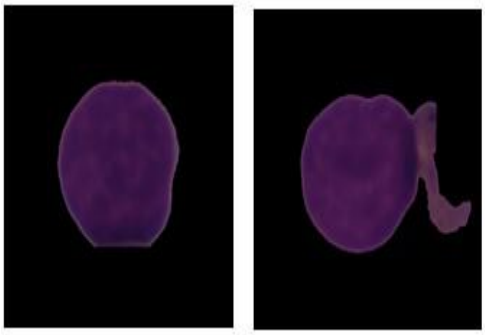

Fig.2: ALL cell microscopic images from the dataset (close visual similarity).

4.2 Data Pre-Processing and Preparation

All the images in the dataset were cropped from their original size of 450∗450 pixels to 400∗400 pixels to retain the maximum amount of information when resizing the images. The images were then resized to 300∗300∗3. The dataset was split into training and testing data with a ratio of 8:2. Further the training data was augmented by performing random augmentations such as rotations, horizontal flips and vertical flips to increase the amount of training samples and to reduce over-fitting.

4.3 Network Architecture

For training purpose considering the low variance of the data set consistent increase in filter size was applied. A 14-layer convolution model was devised where each layer was followed by a batch normalization layer to reduce the discrepancy between the weight matrices of feature maps.Also, a max pool layer followed where the filter size changed between two layers due to memory constraints and for simplified computation.The output of the convolution model was vectored and two fully connected layers with dropout rate of 0.3 and neurons equal to 4096 and 1000 respectively were added for prediction purpose.The output layer was another fully connected layer activated using a softmax function for

final classification. The Network architecture diagram of is as shown in figure 3 and the detailed layer configuration is given in table 2.

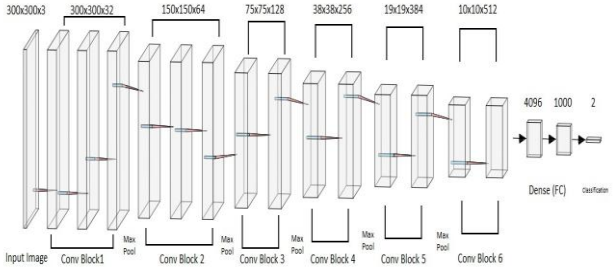

Fig.3: Network Architecture

Table 2: Model Architecture

Block	Layer	Input Size	No. of Filters	Filter Size	Output Size
Block 1	Layer 1_1 Layer 1_2 Layer 1_3	300∗300∗3 300∗300∗32 300∗300∗32	32 32 32	3∗3 3∗3 3∗3	300∗300∗32 300∗300∗32 300∗300∗32
Block 2	Layer 2_1 Layer 2_2 Layer 2_3	150∗150∗32 150∗150∗64 150∗150∗64	64 64 64	3∗3 3∗3 3∗3	150∗150∗64 150∗150∗64 150∗150∗64
Block 3	Layer 3_1 Layer 3_2	75∗75∗64 75∗75∗128	128 128	3∗3 3∗3	75∗75∗128 75∗75∗128
Block 4	Layer 4_1 Layer 4_2	38∗38∗128 38∗38∗256	256 256	3∗3 3∗3	38∗38∗256 38∗38∗256
Block 5	Layer 5_1 Layer 5_2	19∗19∗256 19∗19∗384	384 384	3∗3 3∗3	19∗19∗384 19∗19∗384
Block 6	Layer 6_1 Layer 6_2	10∗10∗384 10∗10∗512	512 512	3∗3 3∗3	10∗10∗512 10∗10∗512
FC(4096)					
FC(1000)					
FC(2)					

4.4 Network Training

Activation functions used for hidden layers were Non-Linear activation functions Relu and Sigmoid. The activation function used for the output layer was Probabilistic activation function Softmax. Further padding was set to Same. During training, SGD optimizer used was found to be performing best at the learning rate of 0.0002. The epochs were set to 100 and the batch size to 60. In order to reduce over-fitting and increase accuracy of the model on test data regularization technique was used. An l2 regularizer at 0.02 was applied with each layer and Binary Cross-Entropy was used as the loss

function. Also, callbacks were set to obtain the best possible parametric values. All the training and validation operations were performed on an Ubuntu 18.04 system (with two 1080ti GPUs), employing Keras (ver. 2.2.4) with Tensorflow (ver. 1.13.1) backend.

4.5 Binary Cross-Entropy Loss

Also called Sigmoid Cross-Entropy loss, it is a Sigmoid activation plus a Cross-Entropy loss. Unlike Softmax loss it is independent for each vector component (class), meaning that the loss computed for every CNN output vector component is not affected by other component values. That is why it is used for multi-label classification, were the insight of an element belonging to a certain class should not influence the decision for another class. It's called Binary Cross-Entropy Loss because it sets up a binary classification problem between two classes.

The Binary Cross-Entropy loss function is as follows:

$$L = -\frac{1}{N} * \sum_{i=1}^{N} yi \ * log(p(yi)) + (1 - yi) * log(1 - \ p(yi))$$

where *y* is the label and *p(y)* is the predicted probability of the data point belonging to one of the two classes for all *N* points. The Cross-entropy loss function was used because of the data being images and the value for each pixel is restricted between 0 & 1 due to batch normalization.

5 RESULTS

The performance metric selected for model evaluation was accuracy. There are four possible outcomes of a classifier: true positives (when cancerous cells are correctly classified), true negatives (when non-cancerous cells are correctly identified), false positives (when non-cancerous cells are classified as cancerous) and false negatives (when cancerous cells are classified as non-cancerous).

$$Accuracy = \frac{No.of\ correct\ predictions}{Total\ no.of\ predictions}$$

Callbacks were chosen to monitor the validation accuracy and save the model at best possible parametric weights. Considering the simplicity of the model architecture, an accuracy rate of 89.72 was achieved. Table 3 shows the performance comparison of the various different models and our model.

Table 3: Performance Comparison

Architecture	Accuracy (%)
AlexNet	81.62
VGG16	84.8
ResNet50	84.77
InceptionV3	83.67
Proposed Model	**91.41**

Ablation Study

Generalization. If the said model is tested on a dataset that is in effect different, or does not follow the same image acquisition and pre-processing standard as that of the training data the model does not perform well.

CONCLUSION

Our results conclude that a simple architecture can be devised which classifies our data with more precision and accuracy. The classical architectures fail mainly due to high invariance in the dataset and thus being incapable of effective feature selection and classification. The main advantage of this model is that it is computationally efficient compared to the much complex architectures. The model also continues to grow effectively as the epochs are increased.

We also found out that the of all the optimizers used, SGD gave the best classification result in all the configurations at a learning rate of 0.0002. ReLU, Sigmoid function was used as the activation functions for the convolution network layers and Softmax function was used as the activation function for the last Fully Connected (FC) layer for classification.

Future Work

The results can further be improved by combining various similar models in an ensembling technique. Also,auto-encoders can be applied for weight matrix initialization. Implementing the same model with greater number of epochs in a faster GPU system might also enhance the models functionality. Further, additional image processing techniques may also be explored for data preparation. Standardizing the image acquisition and pre-processing standards can, in effect, make the model universally applicable.

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